American Academy of Ophthalmology
The Eye M.D. Association

Long-Term Effects of Tocilizumab Therapy for Refractory Uveitis-Related Macular Edema

Marina Mesquida, MD,[1] *Blanca Molins, PhD,*[2] *Victor Llorenç, MD, PhD,*[1] *Maite Sainz de la Maza, MD, PhD,*[1] *Alfredo Adán, MD, PhD*[1]

Objective: To report the long-term efficacy and safety of the interleukin-6 receptor antagonist tocilizumab for refractory uveitis-related macular edema (ME).

Design: Retrospective cohort study.

Participants: Eyes with uveitis seen at a single tertiary referral center for which ME was the principal cause of reduced visual acuity.

Methods: Data were obtained by standardized chart review.

Main Outcome Measures: Central foveal thickness (CFT) measured by optical coherence tomography, degree of anterior and posterior chamber inflammation (Standardization of Uveitis Nomenclature Working Group criteria), and visual acuity (logarithm of the minimum angle of resolution [logMAR]) were recorded during tocilizumab therapy at months 1, 3, 6, and 12.

Results: Eleven eyes from 7 patients (all women) were included. Mean age was 43.4 years. Mean duration of ME was 14.2 years. Mean follow-up with tocilizumab therapy was 15.2 months (range, 12−18 months). Before tocilizumab therapy, conventional immunosuppressive therapy and 1 or more biologic agents failed in all patients. Uveitis diagnoses were birdshot chorioretinopathy (n = 3), juvenile idiopathic arthritis-associated uveitis (n = 3), and idiopathic panuveitis (n = 1). Mean CFT was 550±226 μm at baseline, 389±112 μm at month 1 ($P = 0.007$), 317±88 μm at month 3 ($P = 0.01$), 292±79 μm at month 6 ($P = 0.006$), and 274±56 μm at month 12 of follow-up ($P = 0.002$). Mean logMAR best-corrected visual acuity improved from 0.67±0.53 at baseline to 0.4±0.56 at month 12 ($P = 0.008$). Tocilizumab therapy was withdrawn in 2 patients because of sustained remission at month 12. In both patients, ME relapsed 3 months after tocilizumab withdrawal. Reinitiation of tocilizumab therapy led to good uveitis control and ME resolution. Tocilizumab generally was well tolerated and no serious adverse events were reported.

Conclusions: In this study, tocilizumab was effective in the treatment of refractory inflammatory ME. No serious adverse events were observed. *Ophthalmology 2014;121:2380-2386 © 2014 by the American Academy of Ophthalmology.*

Macular edema (ME) is the leading cause of visual loss in uveitis patients.[1] The pathogenesis of ME involves disruption of the blood−retinal barrier, followed by both intracellular and extracellular fluid accumulation within the macular retina.[2] Despite adequate control of uveitis activity, ME may persist, leading to permanent photoreceptor damage and loss of central visual acuity.[3] After developing, ME either may subside spontaneously or may respond to treatment intended to reduce local inflammatory mediators. In recurrent and chronic forms, systemic treatment should be started, usually consisting of corticosteroids and conventional immunosuppressive drugs.[4] In cases of lack of efficacy or intolerance to classical therapy, biologic agents such as monoclonal anti−tumor necrosis factor α (TNFα) antibodies also may be used.[5] However, despite these treatment options, a number of patients remain refractory and ME may lead to severe visual impairment. Tocilizumab, a fully humanized antibody that binds both to soluble and membrane-bound interleukin-6 (IL-6) receptors, currently is approved for the treatment of rheumatoid arthritis refractory to 1 or more anti−TNFα drugs.[6] Our group previously reported on tocilizumab efficacy in uveitis-associated ME in a 6-month follow-up study.[7,8] Herein we describe the long-term effects of tocilizumab therapy in a case series of patients with long-standing, refractory uveitis-associated ME.

Methods

Study Population

All patients who received tocilizumab (RoActemra; Hoffmann-La Roche, Basel, Switzerland) at the Ophthalmology Institute of the Hospital Clinic of Barcelona, Spain, from January 2012 through December 2013 were included in the study. In all cases, ME was the principal cause of impaired visual acuity. Written informed consent was obtained from patients for off-label use of tocilizumab. Institutional review board approval for the record review was

http://dx.doi.org/10.1016/j.ophtha.2014.06.050
ISSN 0161-6420/14

granted before starting the study. This research adhered to the tenets of the Declaration of Helsinki.

Tocilizumab was administered intravenously at a dose of 8 mg/kg body weight at 4-week intervals. The drug was infused for 1 hour. Potential adverse events monitoring, including completed blood cell count, liver function tests, and vital signs, was performed in all patients before initiating tocilizumab treatment and was repeated before each infusion. All patients were tested for latent tuberculosis by tuberculin skin test before initiation of tocilizumab.

Data Collection

Data were obtained by standardized chart review. Collected data included demographic data such as age, gender, and type of uveitis. Previous and concomitant treatments and follow-up time also were noted. Data on prior and concomitant therapies included use of oral corticosteroids, conventional immunosuppressive drugs, biologic agents, and intravitreal therapies.

Baseline examination included best-corrected visual acuity (BCVA), slit-lamp examination, indirect ophthalmoscopy, and measurement of central foveal thickness (CFT) by spectral-domain optical coherence tomography (OCT; Cirrus HD, Model 4000; Carl Zeiss, Dublin, CA). The macular cube 512×128 protocol was used to obtain the spectral-domain OCT analysis. Inflammatory activity was graded according to the Standardization of Uveitis Nomenclature Working Group grading schemes for the anterior chamber (cells and flare) from grade 0 to 4, representing the level of active inflammation.[9] A modified version of the National Eye Institute system for grading vitreous haze as proposed by the Standardization of Uveitis Nomenclature Working Group was used.[10] Clinical activity of uveitis, including binocular indirect ophthalmoscopy score in the vitreous, was less than 0.5+ in all eyes at the time of initiating tocilizumab treatment. Best-corrected visual acuity was measured with Snellen charts and was converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis.

Outcome Measures

The primary outcome measure was the change in CFT measured with spectral-domain OCT from baseline. Secondary outcomes were changes in logMAR BCVA and evidence of active intraocular inflammation. Treatment results were assessed at 1, 3, 6, and 12 months after initiating tocilizumab infusions.

Statistical Analysis

The effect of tocilizumab was evaluated by changes in CFT and logMAR BCVA. Continuous and 2-measurement interval variables were analyzed with the Wilcoxon signed-rank test, and 3-measurement or more interval variables were tested with the Friedman test. Statistical analysis was performed with SPSS software (PASW for Windows 18.0; SPSS, Inc, Chicago, IL), and we considered a type I error of 0.05. Quantitative variables were described by median and standard deviation, and qualitative variables were described with absolute and relative frequencies. Baseline values before treatment were used as covariates. Inferential analyses were performed using the same methodology by means of a nonparametric approach using a rank transformation of dependent variables. Because this was a retrospective, observational, noncomparative study, all *P* values were considered for descriptive purposes.

Results

Demographics and clinical characteristics of the study population are summarized in Table 1. Seven patients (all women) with uveitis-related ME were included in this study. All patients had bilateral disease. Nevertheless, 11 eyes were included. Three eyes (of patients 1, 2, and 6) were not included in the study because their baseline BCVA was very poor (counting fingers or light perception) and long-standing structural damage precluded any improvement. Mean age was 43.4 years (range, 23−70 years). Uveitis diagnoses were birdshot chorioretinopathy (n = 3), juvenile idiopathic arthritis-associated uveitis (n = 3), and idiopathic panuveitis (n = 1). Before tocilizumab therapy, patients previously had been refractory to high doses of systemic corticosteroids, immunosuppressive drugs, and at least 1 biologic agent other than tocilizumab. Prior immunosuppressive drugs included cyclosporine A in 6 (85.7%) of 7 patients, methotrexate in 3 (42.8%) of 7 patients, and mycophenolate mofetil in 2 (28.6%) of 7 patients. Biologic agents used before tocilizumab therapy were adalimumab in 7 (100%) of 7 patients, infliximab in 2 (28.6%) of 7 patients, rituximab in 2 (28.6%) of 7 patients, and abatacept in 1 (14.3%) of 7 patients. Dexamethasone intravitreal implants were used previously in 7 (63.6%) of 11 eyes, causing a transient response of the uveitic ME.

Macular edema was considered persistent or unresponsive when CFT was more than 350 μm as determined by OCT, despite the use of multiple different systemic or local treatments, or both. Previous biologic therapies were withdrawn and patients had a washout period of at least 3 months before initiating tocilizumab treatment.

Mean duration of ME was 14.3±10.2 years. Figure 1 shows CFT evolution during follow-up. Mean CFT (95% confidence interval) was 550±226 μm in baseline, 389±112 μm at month 1 ($P = 0.007$), 317±88 μm at month 3 ($P = 0.01$), 292±79 μm at month 6 ($P = 0.006$), and 274±56 μm at month 12 of follow-up ($P = 0.002$). Mean BCVA improved from 0.67±0.53 logMAR in baseline to 0.4±0.56 logMAR at month 12 ($P = 0.008$; Fig 2). After 6 months of tocilizumab therapy, a statistically significant improvement in BCVA was observed in 9 of 11 eyes ($P = 0.028$), and BCVA remained stable in 2 eyes and worsened in none.

Sustained uveitis remission was maintained in all patients. Tocilizumab therapy was withdrawn in 2 patients (patients 2 and 3) because of ME−sustained remission (defined as CFT <300 μm without cystic spaces on OCT) at month 12. However in both patients, ME relapsed after 3 months of discontinuation and tocilizumab was restarted. A good second response to tocilizumab therapy was observed in both patients, with ME resolution and good uveitis control (Figs 3 and 4). Tocilizumab generally was well tolerated and no serious adverse events were reported. No infusion reactions were noted. Few patients receiving tocilizumab therapy reported a mild fatigue 1 or 2 days after the infusion, but this did not impair their regular activity. As shown in Table 1, all patients were able to taper corticosteroids, conventional immunosuppressive medications, or both during tocilizumab therapy.

Discussion

Interleukin-6 is a key cytokine with redundant roles and pleiotropic activity in initiating and propagating immune responses in human inflammatory disease.[11] Production of IL-6 in inflamed tissues induces excess of vascular endothelial growth factor, which causes increased angiogenesis and vascular permeability, leading to vascular leakage and an influx of cytokines and inflammatory cells.[12] Interleukin-6 also plays an important role in cell proliferation and